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The duality of macrophage function in Chronic Lymphocytic Leukaemia

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Abstract

Chronic lymphocytic leukaemia (CLL) is the most common adult leukaemia and, in some patients, is accompanied by resistance to both chemotherapeutics and immunotherapeutics. In this review we will discuss the role of tumour associated macrophages (TAMs) in promoting CLL cell survival and resistance to immunotherapeutics. In addition, we will discuss mechanisms by which TAMs suppress T-cell mediated antitumour responses. Thus, targeting macrophages could be used to i) reduce the leukaemic burden via the induction of T-cell-mediated antitumour responses, ii) to reduce pro-survival signalling and enhance response to conventional chemotherapeutics or iii) enhance the response to therapeutic antibodies in current clinical use.

Chronic Lymphocytic Leukaemia (CLL).

Chronic lymphocytic leukaemia is a B cell lineage-derived blood cancer characterised by an accumulation of leukaemic cells within the blood, bone marrow and lymphoid tissues [1]. Whilst the clinical course of CLL is varied, it usually presents as indolent disease which endures for a variable length of time. Conversion of CLL from the quiescent (stable disease) phase to disease requiring treatment (progressing disease) occurs in approximately 70% of patients and is often associated with reduced lymphocyte doubling time, del(17p), TP53 and IKZF3 mutations [2, 3]. Whilst we often refer to CLL as being stable or progressive it may be more realistic to view CLL as a disease that exists on a spectrum spanning "stable" through to disease requiring treatment. We know that CLL development, progression and relapse are accompanied by multiple mutational events [2, 3], but it is also clear that the microenvironment contributes to disease progression and responses to chemo-immunotherapeutic regimes. Of central importance to CLL are interactions between the leukaemic cells and the microenvironment within the bone marrow, lymphoid tissues and the circulation. The CLL microenvironment is shaped by a complex network of cytokines and chemokines, as well as direct interactions of malignant B cells with CD4+ and CD8+ T-cells, NK T-cells, and specialised macrophages often referred to as nurse like cells (NLCs) or tumour associated macrophages (TAMs). A better understanding of the role of the microenvironment and its relationship with leukaemic CLL cells has identified several events with considerable potential for translation into patient treatments. In particular, tumour associated macrophages (TAM) are important contributors to CLL development and progression as well as effectors of antibody-based immunotherapy. In this review we focus on the duality of the roles of TAMs, in particular their pro-tumourogenic and immune-suppressive role in CLL as well as their role as immune effectors of therapeutic antibodies.

Macrophage lineage.

Macrophages are an essential component of the innate immune system and are comprised of resident tissue macrophages as well as monocyte-derived macrophages. Many tissue macrophages are derived from the early embryonic yolk sac or liver [4]. Post-partum, tissue macrophages are either derived *via* self-renewal of resident tissue macrophages or through the attraction and subsequent differentiation of monocytes. In the latter instance, haemopoietic stem cells differentiate into two progenitor cell lineages namely myeloid progenitor cells (myelopoiesis) and lymphoid progenitor cells (lymphopoiesis) [5]. Lymphopoiesis gives rise to B-cells, T-cells and NK-cells whereas myelopoiesis gives rise to erythrocytes, monocytes, granulocytes and platelets [5-7]. Progenitor cells of both lineages give rise to differentiated cells that are released into the bloodstream where they remain or can be induced to undergo further differentiation within specific tissue sites [8-10]. In the post-partum setting, monocytes are derived from macrophage and dendritic cell (DC) progenitor cells (MDPs), which can differentiate into dendritic cells or macrophages in peripheral tissue sites, (**Figure 1**) [11-13]. Activated dendritic cells migrate to secondary lymphoid organs and present antigen to lymphocytes such as T-cells [14, 15], a key event in the initiation of adaptive immune responses. In contrast, macrophages have tissue-specific functions [11, 12, 16-18] and largely remain within the peripheral tissue after activation [9]. Macrophages present antigens and are effectors of Fc gamma receptor (FcγR)-dependent cell elimination *via* antibody-dependent cell mediated cytotoxicity (ADCC) and antibody-dependent

phagocytosis (ADP). More recently, it has emerged that TAMs can suppress T-cell mediated

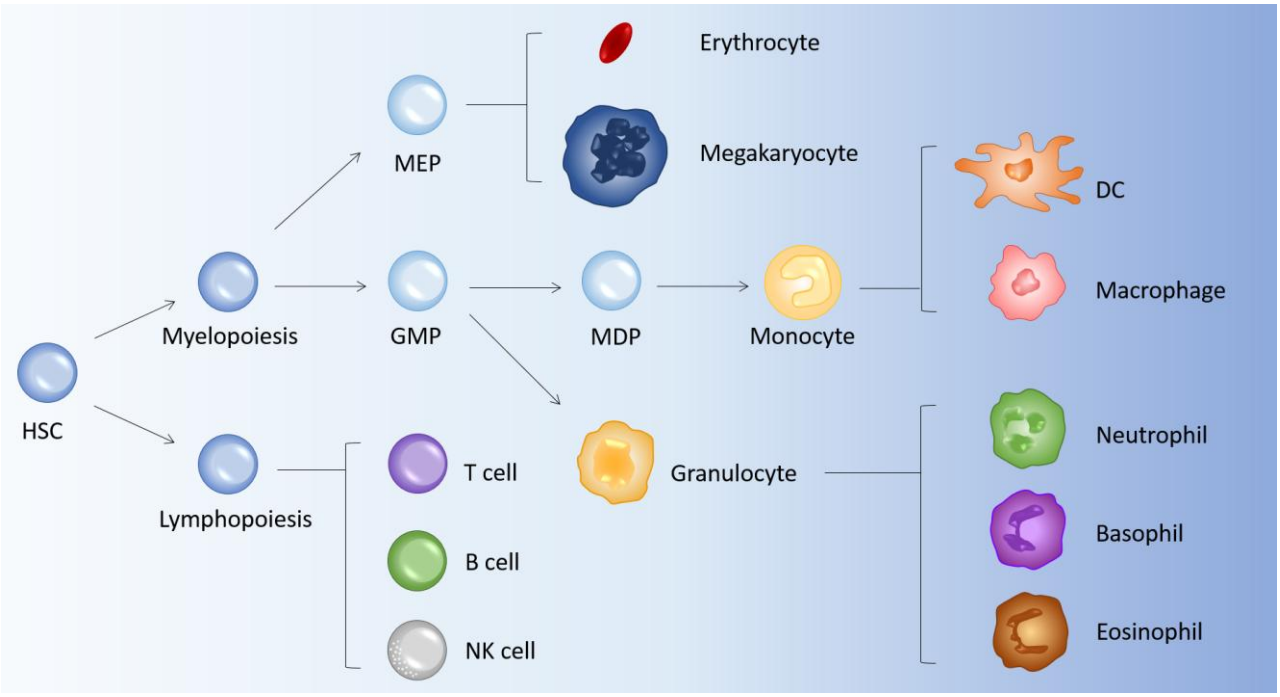

Figure 1. Haematopoietic lineage of macrophages. *The haematopoietic cells in bone marrow differentiate into myeloid (myelopoiesis) or lymphoid progenitor cells (lymphopoiesis). Lymphopoiesis gives rise to B-cells, T-cells and NK-cells whereas myelopoiesis involves two progenitors namely granulocyte–monocyte progenitors (GMPs) and megakaryocyte-erythrocyte progenitors (MEPs). Macrophage and dendritic cell progenitor cells (MDPs) give rise to monocytes which in turn differentiate into dendritic cells (DCs) and macrophages after recruitment to peripheral tissue sites.*

antitumour responses *via* PI3Kγ mediated immune response [19, 20]. In addition, macrophages regulate tissue homeostasis through the modulation of metabolism, tissue damage sensing, and tissue remodelling [11, 16].

Whilst macrophages are traditionally thought as phagocytes with activity against infectious particles and cancer cells, it has become evident that multiple macrophage phenotypes exist that display a wide repertoire of functional capabilities [21]. Macrophages are classified by the expression of cell surface markers and their functional activation status. Classically, macrophages activated by IFNγ or microbial components were referred to as M1 macrophages [22], which release pro-inflammatory cytokines (TNF-a, IL-12) and activate T-cells. On the other hand, M2 macrophage-phenotypes were induced by IL-4/IL-13 and characterised by anti-inflammatory effector molecules (IL-10, TGF-beta, HO-1, and arginase) that modulate inflammatory responses, and control wound healing and tissue regeneration [22]. More recently, it has become accepted that macrophages display considerable phenotypic plasticity where the experimentally induced “M1”-like and “M2”-like phenotypes are the extreme ends of the spectrum [21]. Macrophages phenotypically adapt to suit the microenvironment in response to various stimuli and cytokines. For example, within an infectious microenvironment macrophages may acquire an “M1” state whereas within cancerous tissue there are different cues that induce “M2”-like properties [23-25]. Multiple

studies have shown that the diversity and nature of the macrophage infiltrate in tumours may have either negative or positive prognostic implications depending on the tumour type [26-28]. This suggests that the infiltration of macrophages into a tumour is not only dependent on the tumour type but is dependent on, and may in turn modify, the behaviour of the tumour. These observations suggest that macrophages can potentially both promote the survival of tumour cells (pro-tumourogenesis) whilst also being mediators of tumour cell killing. Indeed, recent studies have shown that the pro-tumourogenic and immunosuppressive properties of tumour associated macrophages can be modulated by the PI3K/mTOR pathway which is actionable using clinically available agents [29, 30]. Thus, tracking macrophage phenotypes in the context of malignancy will be informative since it can provide an assessment of whether the malignant cells exist within the context of a pro- or anti-tumourogenic environment which may guide targeted therapies [31, 32]. It is this paradox that makes macrophages such a compelling target for anticancer therapies [31, 33].

The role of macrophages in CLL pathogenesis

Macrophages both support the functioning of normal tissue-specific parenchymal cells and malignant cells, and are dependent on the signals generated by the parenchymal cells in the local environment [11, 22, 34, 35] for their differentiation. In CLL, evidence supports a "symbiotic" relationship between the malignant CLL cells and tumour associated macrophages, (**Figure 2**). For example, TAMs are required to maintain the survival of the malignant B cells within the bone marrow [36-39].

During conversion from the normal to neoplastic state, B cells start to secrete factors that attract circulating monocytes into the developing tumour niche [40] and induce them to differentiate into macrophages, which are characterised by high expression of surface markers such as CD14+, CD68, CD163 and CD206 [37, 41], consistent with an "M2"-like phenotype and functionality [27]. These macrophages have been shown to be functionally and transcriptomically indistinguishable from NLCs [42-45]. The term NLC specifically refers to *in vitro* cultures of monocyte-derived M2-like macrophages isolated from PBMCs and are the functional equivalent of TAMs located *in vivo* within CLL tissues (ie NLCs = CLL-specific TAMs)[36]. NLCs are generated following the *in vitro* co-culture of CD14+ monocytes from either healthy donors or CLL patients with CD19+ CLL cells. In these cultures, the CLL cells induce NLC differentiation, which is accompanied by the production of cytokines by NLCs that promote the survival of the CLL cells [41] (**Figure 2**). Significantly, B cells from healthy donors are incapable of inducing a NLC phenotype in monocytes, and these monocytes do not support the survival of CLL cells [41]. Thus, malignant CLL cells induce the differentiation of NLCs which, in turn, secrete factors that promote the survival of the CLL cells. This indicates that targeted depletion of NLCs (or their *in vivo* equivalent, CLL-specific TAMs) may be a potential therapeutic strategy to reduce the leukaemic burden in CLL patients.

Due to the critical nature of the CLL:NLC interaction, identifying the secreted factors and membrane receptors that co-ordinate these events has been the subject of much study. Notably, this interaction appears to be independent of direct cell-to-cell contact [37, 41, 46, 47]. For example, *in vitro* studies using transwell-culturing systems, in which the NLCs and CLL cells are separated by a

membrane, showed that direct contact of NLCs to CLL cells was not required for the pro-survival signals from the NLCs [46]. The tissue niche of CLL comprises a complex cocktail of cytokines and chemokines that induce a prosurvival signal to CLL cells [46, 48-50]. These cytokines and chemokines play a crucial role in driving the 'symbiotic' relationship and are derived from the CLL cells, monocytes, TAMs/NLCs, as well as accessory stromal cells. For example, interleukin-4 (IL-4) [51, 52], IL-13 [53] and IL-10 [54] are secreted by CLL cells and promote M2-like properties in monocytes and NLCs. Significantly, the M2-like phenotype has been linked to localised immunosuppression mediated *via* reduced T-cell infiltration and T-cell mediated anti-tumour responses [20, 29]. The M2-like NLCs activate pro-survival responses in CLL cells *via* secreted factors such as insulin-like growth factor-1 (IGF-1) [55, 56], IL-8 [57], CCL2 [49] and CXCL12 [58] thereby stimulating an increased leukaemic burden. The leukaemic burden within the tissue niche is further increased by the continued recruitment of circulating monocytes to the CLL niche resulting in differentiation to M2-like NLCs induced in a microenvironment rich in chemokines such as CCL3, CCL4 [59], CCL2, CXCL12, CXCL13, CXCL19 and CXCL20 [60]. In particular, high levels of CCL3 and CCL4 in the CLL environment have been shown to attract monocytes *via* signalling through CCR1 and CCR5 [61]. Recruitment to the tumour niche is further enhanced by the binding of CCL2 to CCR2 and CCR4 on tissue-resident macrophages and the subsequent activation of migration [61]. Thus, the tumour niche is a self-sustaining immune suppressive environment in which leukaemic cells encourage an increase in the numbers of M2-like NLCs/TAMs, which provide pro-survival factors for the CLL cells as well as suppress anti-tumour immunity within the CLL microenvironment.

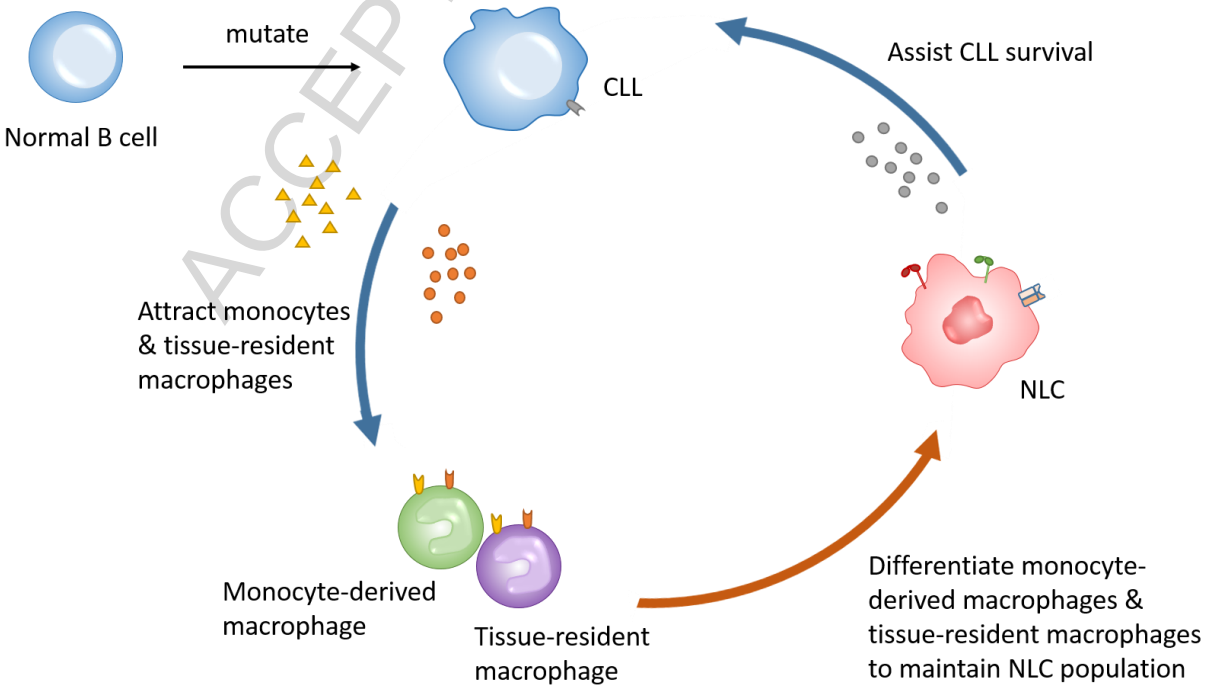

Figure 2. Symbiotic relationship between CLLs and TAMs/NLCs. *Chronic lymphocytic leukaemia (CLL) originates from transformed B cells that exist in a symbiotic relationship with accessory NLC cells. CLL & NLCs create a microenvironment that attracts and skews macrophages to acquire an M2-phenotype. Chemo-attractants secreted by CLLs recruit tissue-resident macrophages and newly matured monocyte-derived macrophages to the CLL niche where they acquire the M2-like phenotype (NLCs). The NLCs then secrete cytokines and chemokines which in turn provide prosurvival signals for CLLs and hence the cycle continues.*

TAMs/NLCs as a therapeutic target

Two major activities attributed to NLCs/TAMs are, 1) the capability to induce pro-tumour survival signals and 2) an ability to dampen/suppress T-cell mediated anti-tumour immunity [19, 20, 62-64]. TAMs associated with the bone marrow trephines from CLL patients display M2-like macrophage markers [46-48, 65]. The pro-survival signals for the CLL cells detailed in the preceding section also induce resistance of CLL cells to chemotherapeutics and suppress T-cell mediated anti-tumour immunity [20, 29, 37]. The critical dependence of CLL cell survival upon TAMs/NLCs was elegantly illustrated by Galletti et al. [66], who demonstrated that liposomal bisphosphonate (Clodrolip) or CSF1R signalling blockade in CLL mouse models depleted tissue macrophages resulting in the loss of TAMs and subsequent death of malignant B cells *via* the TNF pathway. This had the net effect of reprogramming the tumour microenvironment to an anti-tumorigenic state [63, 67]. It is worth noting that non-liposomal formulations of bisphosphonates are in widespread use for osteoporosis and treatment of lytic bone metastases without adverse immune effects. Finally, an independent study recently confirmed these findings and suggested that disruption of the macrophage-malignant cell axis by inhibition of macrophage Lyn/BTK could inhibit the pro-survival (nurse-like) properties of macrophages resulting in reduced CLL burden [39]. Thus, direct targeting of the NLC/TAMs within the CLL microenvironment remains a potentially valuable, yet untested, treatment for reducing CLL tumour burden in patients.

Another implication of targeting TAMs/NLCs is the potential to remove a major immunosuppressive stimulus from the tumour microenvironment. In particular, it has been noted that TAMs possess a PI3Kγ-dependent immune suppressor phenotype which is independent of an additional role in permitting immune checkpoint activity within the tumour microenvironment [19, 68]. Recognition of these new roles of M2-like TAMs supports studies focusing on "driving" the macrophage phenotype towards a more "M1" phenotype [69, 70] rather than ablating all macrophages [20, 30, 68]. For example, recent studies in models of pancreatic cancer and melanoma have shown that targeted inhibition of PI3Kγ by pharmacological inhibitors or genetic depletion of macrophage PI3Kγ promoted the conversion of M2-like TAMs to an M1-like phenotype [29, 52, 63]. The net effect of this was to increase activated T-cell infiltrates within the tumour resulting in reduced tumour load due to a T-cell mediated anti-tumour response [20, 29]. Complementing this, recent studies determined that the enhanced anti-tumour responses that occurred following inhibition of macrophage PI3Kγ were associated with increased expression of immune checkpoint molecules [52, 63]. Finally, it was shown that a combination of a PI3Kγ inhibitor plus an immune checkpoint inhibitor was able to induce significantly enhanced tumour clearance in multiple tumour models [52, 63]. These data suggest that targeted inhibition of the tumour suppressive properties of TAMs combined with inhibition of immune checkpoint regulation, within the tumour microenvironment is likely to induce significant and durable responses in patients. Potential off-target effects of such therapies may include autoimmune disease and altered responses to infection, which could potentially limit their application. However, early studies with immune checkpoint inhibitors alone or PI3K inhibitors alone suggests these effects may be manageable. Thus, it is reasonable to hypothesise that targeted reprogramming of macrophages in the CLL niche could have the potential to transform management of CLL.

Bruton's tyrosine kinase (BTK) inhibitors such as ibrutinib, have shown great promise in CLL with durable responses in both relapsed/refractory [71] disease and as an initial treatment [72]. Whilst these effects are generally attributed to the action of BTK inhibition on BCR function and B cell survival there is emerging evidence that part of their success is attributable to effects on macrophages and other immune effector cells [73, 74]. For example, evaluation of blood samples and bone marrow trephines from a phase II study of 80 patients receiving ibrutinib showed marked reductions in multiple cytokines such as CCL3, CCL4 & CXCL13 [73]. These cytokines are required for recruitment of macrophages to the CLL niche [73]. Thus, reduced recruitment will result in reduced pro-survival sigaling and hence reduced leukemic burden. In addition, examination of bone marrow trephines from ibrutinib treated patients revealed reduced interaction between CLL cells and TAMs [73]. Finally, Boissard noted that NLCs protected CLL cells from the apoptotic effects of therapeutic concentrations of ibrutinib *in vitro* [74]. Combined, these data suggest that the direct anticancer activity of ibrutinib on CLL cells may be aided by i) a reduced ability to recruit TAMs to the CLL niche and ii) an inhibition of direct CLL:TAM interaction. This would result enhanced the therapeutic response to ibrutinib due to the reduced prosurvival signal present within the CLL niche.

Macrophages as an immune effector of therapeutic antibodies.

In the previous sections we discussed the pro-survival and immunosuppressive roles of NLCs/TAMs in CLL. These highlighted the therapeutic potential of targeting NLCs/TAMs as a means of reducing the leukaemic burden or activating T-cell mediated antitumour responses. However, NLCs/TAMs are also potent mediators of antibody-dependent immune responses. Antibodies induce cytotoxic effector functions of innate immune cells such as antigen-dependent phagocytosis (ADP) and antigen-dependent cell mediated cytotoxicity (ADCC) mediated by both macrophages and NK-cells [75, 76]. Monoclonal antibodies are an important component of therapy for CLL and thus preserving or enhancing existing macrophage function may, paradoxically, be of benefit to CLL patients.

IgG antibodies display diversity in their antigen-binding Fab domains. There is also diversity in the IgG Fc domain, which facilitates binding to immune effector cells [77]. Monoclonal antibodies for clinical use in CLL have been developed against CD20, CD47, CD52 and CD62L epitopes [42, 76, 78, 79]. Diversity in the structure of these IgG antibodies, particularly the Fc region, results in a spectrum of immune responses directed against antibodies bound to the malignant cell. Responses include complement-dependent cytotoxicity, phagocytosis, as well as cell-mediated cytotoxicity by NK cells, neutrophils, monocytes, macrophages, dendritic cells, and eosinophils [76, 79, 80]. Further work remains to be undertaken to fully characterise the spectrum of effector functions elicited by each monoclonal antibody. However, it is clear from murine models [76, 81] and human studies [80] that monocytes and macrophages are dominant effector cells in some settings. For example, the induction of an immune response to different engineered antibodies was shown to be dependent upon the binding affinity for the Fc receptors expressed by macrophages [82]. Time-lapse fluorescence video microscopy imaged CLL cells treated with an anti-CD62L antibody and revealed rapid binding of the target CLL cells to the NLCs derived from CLL patients. These bound CLL cells were rapidly internalised and killed by the NLCs [83]. Given the efficiency with which the macrophages can mount a cytotoxic response to therapeutic antibodies it is surprising that

tumour clearance is not profound and durable. However, it is clear that, as with most therapeutic antibodies in use today, that acquired or inherent resistance can develop which significantly reduces their current clinical efficacy.

Macrophage-mediated therapeutic antibody resistance in CLL.

Similar to other cancers, inherent and/or acquired resistance to therapeutic antibodies is common in CLL, and in the relapsed setting, is a significant challenge in treating CLL patients [84, 85]. Recently, we and others have made significant progress in understanding the molecular mechanisms that drive resistance to therapeutic antibodies in CLL. Therapeutic monoclonal IgG antibodies bind to their cognate target on CLL cells to form an immune complex that is recognised by, and binds to, type I Fc receptors (FcγR) on macrophages. This interaction with a tumour-specific immune complex is the basis for the anti-tumour activity of macrophages. Thus, it is important to understand FcγR biology in the context of a major immune effector cell type, the macrophage, in order to understand resistance mechanisms. To date, six different classes of FcγRs (FcγRI, FcγRIIA, FcγRIIB, FcγRIIC, FcγRIIIA and FcγRIIIB) have been described. Activating FcγRs comprise FcγRI, IIa, IIc, IIIa and IIIb, and induce ADCC/ADP *via* a cascade of signalling events involving Lyn, Syk, PI3K and Btk activation/phosphorylation [67, 75, 86, 87]. In contrast, FcγRIIb inhibits ADCC/ADP tumour cell killing *via* activation of phosphatases such as Ship1/2, which catalyse the conversion of PIP3 to PIP2 thus blocking FcγR-dependent activation [88, 89] (**Figure 3**). Hence, FcγR-dependent events (e.g. ADCC or ADP) are controlled by the balance between activating (referred to collectively as ITAM) and inhibitory (referred to as ITIM) signalling pathways within the effector cells. Most importantly, ADCC and ADP responses to therapeutic antibodies are determined by the ratio of ITAM/ITIM signalling pathways [42, 77, 90]. For example, a low ITAM/ITIM ratio would reflect a poor response and a high ITAM/ITIM ratio would favour a good

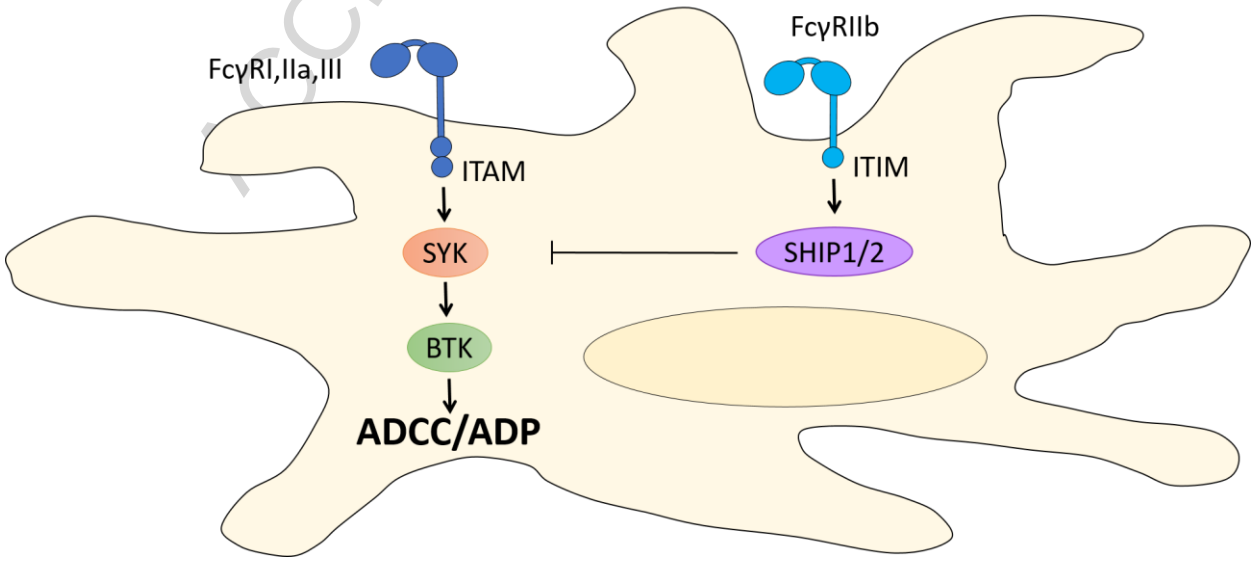

Figure 3. FcγR signalling pathway in NLCs/TAMs*. Diagram illustrates the FcγR activating pathway (ITAM) and the opposing inhibitory (ITIM) pathway present in NLCs derived from CLL patients. Signalling through ITAM is favoured in patients with stable disease whereas patients with progressive disease display reduced ITAM signalling resulting in increasing dominance of FcγRIIb-dependent ITIM signalling.*

therapeutic response to antibodies [42].

Interventions that increase the ITAM/ITIM ratio would be predicted to induce considerable therapeutic benefits. This concept was exploited with the development of the glyco-engineered anti-CD20 antibody, obinutuzumab, which was designed to display a bias for binding activating FcγRs and in this way favour an ADCC response [77, 91]. More recently, we have shown that NLCs derived from patients with progressive disease are less effective at facilitating monoclonal antibody mediated CLL cell cytotoxicity compared to NLCs derived from patients with stable disease. This was attributable to a loss of signalling through the ITAM pathway resulting in increased dominance of signalling through the ITIM pathway and a reduced capacity to participate in ADCC and ADP in response to a therapeutic antibody. Significantly, this was an actionable event since treatment of antibody-resistant CLL patients' PBMCs with a SHIP1 inhibitor resulted in the reinstatement of ADCC and ADP responses to therapeutic antibodies [42] (**Figure 3**). These data suggest that targeting FcγRIIb function with small molecular weight compounds (eg SHIP1/2 inhibitors) or a therapeutic antibody targeting the FcγRIIb receptor [92] may be of clinical value in enhancing therapeutic antibody responses.

Conclusion

NLCs are a specialised form of TAM found in the microenvironment that play a dual role in CLL. In the first instance, NLCs provide survival signals and impair T-cell mediated tumour immunity, thereby contributing to the survival of the malignant B cells in their tissue niche. Targeted ablation of NLCs has been shown to reduce tumour burden in experimental models of CLL thus highlighting their potential importance as a therapeutic target. In addition, targeting the TAM-dependent immune suppression using PI3Kγ inhibitors in models of CLL has also shown *in vivo* activity. However, NLCs have also been shown to be critical effectors of the response to existing chemo-immunotherapeutic combinations used in the treatment of CLL. Significantly, resistance to therapeutic antibodies is an acquired phenotype of NLCs and can be reversed with SHIP1 inhibitors. Thus, targeting TAMs/NLC function is a novel therapeutic strategy that could directly a) remove pro-survival cues from the CLL microenvironment, b) stimulate macrophage-dependent and T-cell mediated antitumour responses and c) optimize responses to existing therapeutic antibodies.

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